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Synthesis of Polyglycerol, Porphyrin-Cored Dendrimers Using Click Chemistry

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Polyglycerol, porphyrin-cored dendrimers were synthesized by the click reaction of azide-cored polyglycerol dendrons and octa-alkynylporphyrin **19**. The dendrons were synthesized divergently starting with TBDPS-protected allyl alcohol **2**. Two, three and four cycles of dihydroxylation-allyl etherification gave dendrons [G-2.5] **6**, [G-3.5] **8**, [G-4.5] **11**, with four, eight, and sixteen alkene groups, respectively. Dendron **11** was readily prepared on large scale with an overall yield of 45 %. Dendron **8** was deprotected and converted into the corresponding alkyne – and azide-cored dendron **13** and **15** in 89 % and 75 % yield, respectively. Dendron **11** was deprotected and converted into the corresponding alkyne – and azide-cored dendron **16** and **18** in 68 % and 24 % yield, respectively. Both the [G-3.5]-azide **15** and [G-4.5]-azide **18** were separately "clicked" to polyalkyne core **19** via the Huisgen 1,3-dipolar cycloaddition to afford **20** and **21** in 65 % and 66 % yield, respectively. Dendrimer **21** has a MW of ca. 16000 and 128 peripheral alkene groups.

Introduction

Polyethylene glycol and materials derived from it continue to attract attention because of their applicability in the fields of biotechnology and pharmacology.[1,2] The properties of polyethylene glycol that make it among the most useful polymers for biomedical applications include: reactive chain ends, excellent water solubility, and a high level of biocompatibility.

A wide range of polyethylene glycol-derived materials and their analogs have been developed with considerable interest in new architectures that may afford new and useful properties. Particularly interesting in this regard are the polyglycerol dendrimers, which have been explored as potential drug delivery agents,[3–6] as pH-responsive molecular nanocarriers[7] and as soluble polymeric supports.[8,9]

The synthesis of these dendrimers was developed by Haag and co-workers using an iterative two-step process consisting of allylation using sodium hydroxide and allyl chloride followed by catalytic dihydroxylation.[10] The dendrimer was efficiently constructed in a divergent strategy that started with a triol core. To the best of our knowledge the synthesis had not been reported using core structures that would leave functionality at the focal point.[11] We were attracted to the possibility of using reactive groups at the focal point to directly link polyglycerol dendrons to functional cores. Although several other promising syntheses of aliphatic polyether dendrimers have appeared in the literature,[12–14] our favourable experience with the Haag synthesis led us to pursue this general approach.[15]

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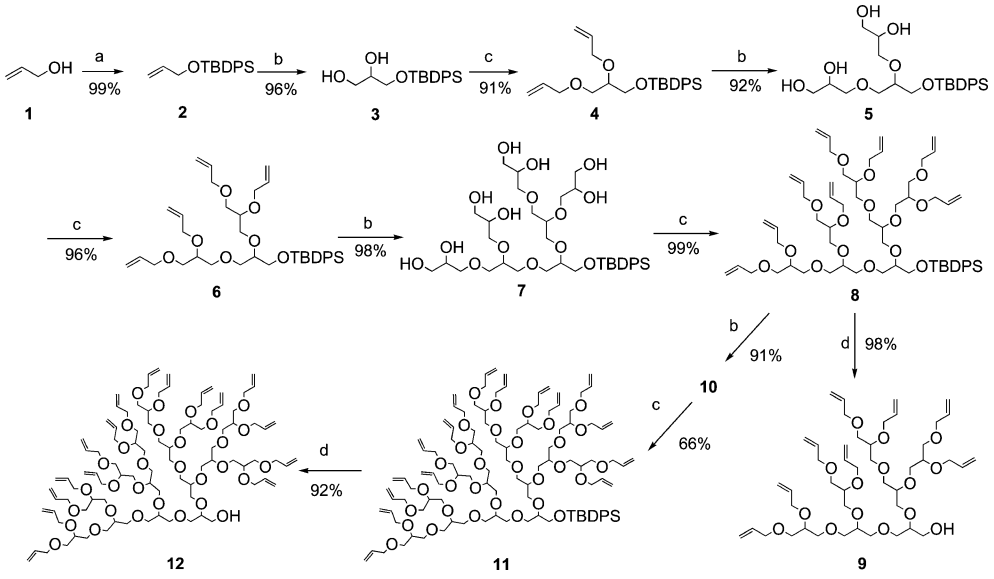
Given the high yields reported in the preparation of dendrimers using the Huisgen 1,3-dipolar cycloaddition ("click") reaction,[16–19] we sought to synthesize polyglycerol dendrons with either azide or alkyne focal points. The goal was to enable attachment of biocompatible polyglycerol dendrons to a wide variety of materials, surfaces, or molecular core units. In preparing the dendrons, it was necessary to find a protecting group sufficiently robust to withstand the highly basic and oxidative conditions required for divergent growth. A number of protecting groups were considered and the most promising based on ease of synthesis and overall yield was the *tert*-butyldiphenylsilyl (TBDPS) group.[20]

Herein we report the scalable synthesis of polyglycerol dendrons [G-3.5]-**8** and [G-4.5]-**11**, with eight and sixteen peripheral alkene groups, respectively, and a single TBDPS-protected alcohol group at the core. Both **8** and **11** were deprotected and converted into the corresponding alkyne- and azide-cored polyether dendrons. The azide-cored dendrons readily underwent copper-catalyzed 1,3-dipolar cycloaddition reaction with an octa-alkynyl tetraaryl-porphyrin. Using this approach, dendritic porphyrins with molecular weights close to 16000 were synthesized.

Results and Discussion

The synthesis of TBDPS-protected dendrons [G-2.5] **6**, [G-3.5] **8**, and [G-4.5] **11** and their deprotection is outlined in Scheme 1. The synthesis began with allyl alcohol, a commercially available and inexpensive starting material which underwent TBDPS protection to provide **2** in high yield as described by Carreira.[21] The dihydroxylation step employed catalytic osmium tetroxide and *N*-methylmorpholine



Scheme 1. a) TBDPS-Cl, imidazole, DMF; b) OsO_4, NMO, acetone, water, *tert*-butyl alcohol; c) allyl bromide, NaH, TBAI, DMF; d) TBAF, THF.

oxide (NMO) as cooxidant.[22] However, it was found that traces of DMF remaining in **2** were problematic, so a silica gel plug was used to remove all traces of DMF. Using material purified in this manner, **3** was obtained in 96% yield. Because of the lipophilic TBDPS group, it was readily separated from unreacted NMO and *N*-methylmorpholine (NMM) byproduct by ethyl acetate extraction.

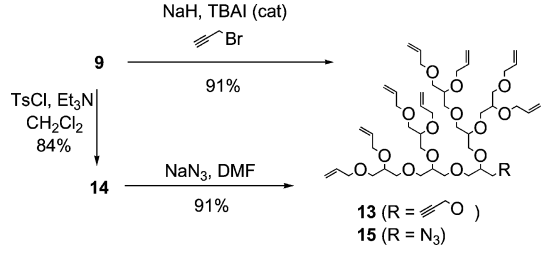
The allylation of **3** employed classical Williamson etherification conditions and was best effected using allyl bromide, sodium hydride, and tetrabutylammonium iodide as a phase-transfer catalyst. Because of the close proximity of the alcohol groups to the silyl group, reaction conditions were chosen to discourage silyl migration.[23] To ensure that silyl migration did not occur, 8 equivalents of allyl bromide per hydroxy group were added to the dendron in a minimal amount of THF prior to the addition of the sodium hydride. In this manner a high concentration of allyl bromide was present and product **4** could be obtained in 91% yield. There was no evidence for any silyl migration in either the ^1H or ^{13}C NMR spectroscopy.

Dihydroxylation of **4** with catalytic OsO_4 proceeded in 92% yield to produce alcohol **5**. After this second cycle dihydroxylation, the product could still readily be purified by extraction into ethyl acetate. Alcohol **5** was allylated to produce dendron **6** in 96% yield followed by dihydroxylation to afford alcohol **7** in 98% yield. The polyhydroxy [G-3]-dendron could not be extracted into ethyl acetate however, repeated extractions using a 9:1 mixture of chloroform to 2-propanol provided a product containing only a small amount of the NMO/NMM impurity by ^1H NMR spectroscopy. Allylation of **7** to afford the [G-3.5]-dendron **8** proceeded in 99% yield. The [G-3.5]-protected dendron **8** was shown to be pure by MALDI-TOF-MS, ^1H NMR and the analytical SEC.

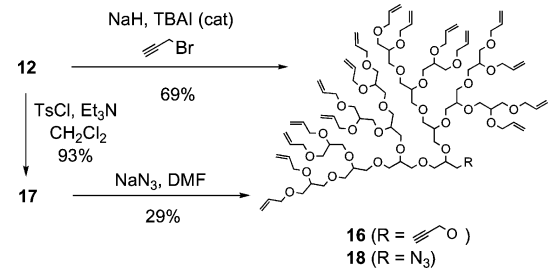
Using the TBDPS protecting group, this scheme has been shown to be amenable to large-scale synthesis. Thus, starting with allyl alcohol, 12 grams of dendron **8** were readily prepared in about one week with a yield of 58% over seven steps. Additionally, it was observed that the dihydroxylation steps could be performed using $K_2OsO_4{\cdot}2H_2O$ instead of OsO_4, and the crude products obtained could be used in the next reaction without purification with no change in yield. The $K_2OsO_4{\cdot}2H_2O$ was less volatile and had a longer shelf-life.

Subsequent dihydroxylation of **8** afforded the [G-4]-dendron **10** in 91% yield. Dendron **10** contained a small amount of NMO impurity even after repeated extractions using a 9:1 ratio of chloroform to 2-propanol. The [G-4]-dendron **10** was found to be insoluble in tetrahydrofuran therefore, it was necessary to run the allylation reaction in DMF. Allylation followed by purification by silica gel chromatography provided product **11** with 16 allyl groups in 66% yield. The material so isolated was shown to be pure by MALDI-TOF-MS, ^1H NMR, ^{13}C NMR and analytical SEC.

It was found that the allylated dendrons were not stable in air at room temperature. The decomposition mechanism or product was not firmly established but the observation of an insoluble gel formation after a few days suggests a free-radical polymerization. Even the [G-1.5]-dendron **4** polymerized after storage open to air at room temperature for



Scheme 2. Synthesis of **13** and **15**.



Scheme 3. Synthesis of **16** and **18**.

several months. As observed by Haag and co-workers,[10] the perallylated dendrons tend to cross-link within several days. Therefore, it was necessary to store these materials in the freezer after backfilling the containers with nitrogen. Using these precautions, it was possible to store the dendrons for up to six months with no observed polymerization.

The focal point of [G-3.5]-ol **9** and [G-4.5]-ol **12** was propargylated by treatment with sodium hydride and propargyl bromide, affording the [G-3.5]-alkyne **13** and [G-4.5]-alkyne **16** in 91% yield and 69%, respectively (Scheme 2 and

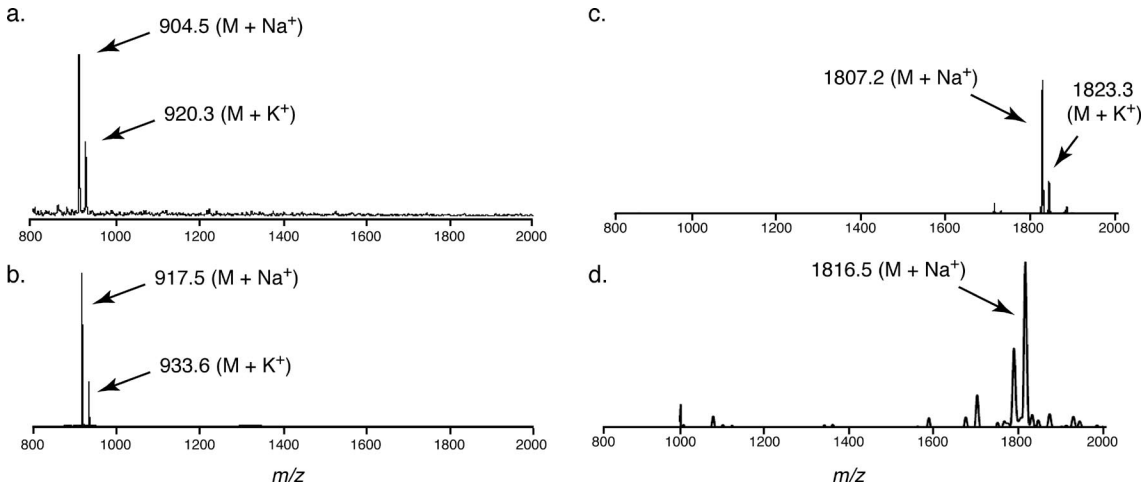
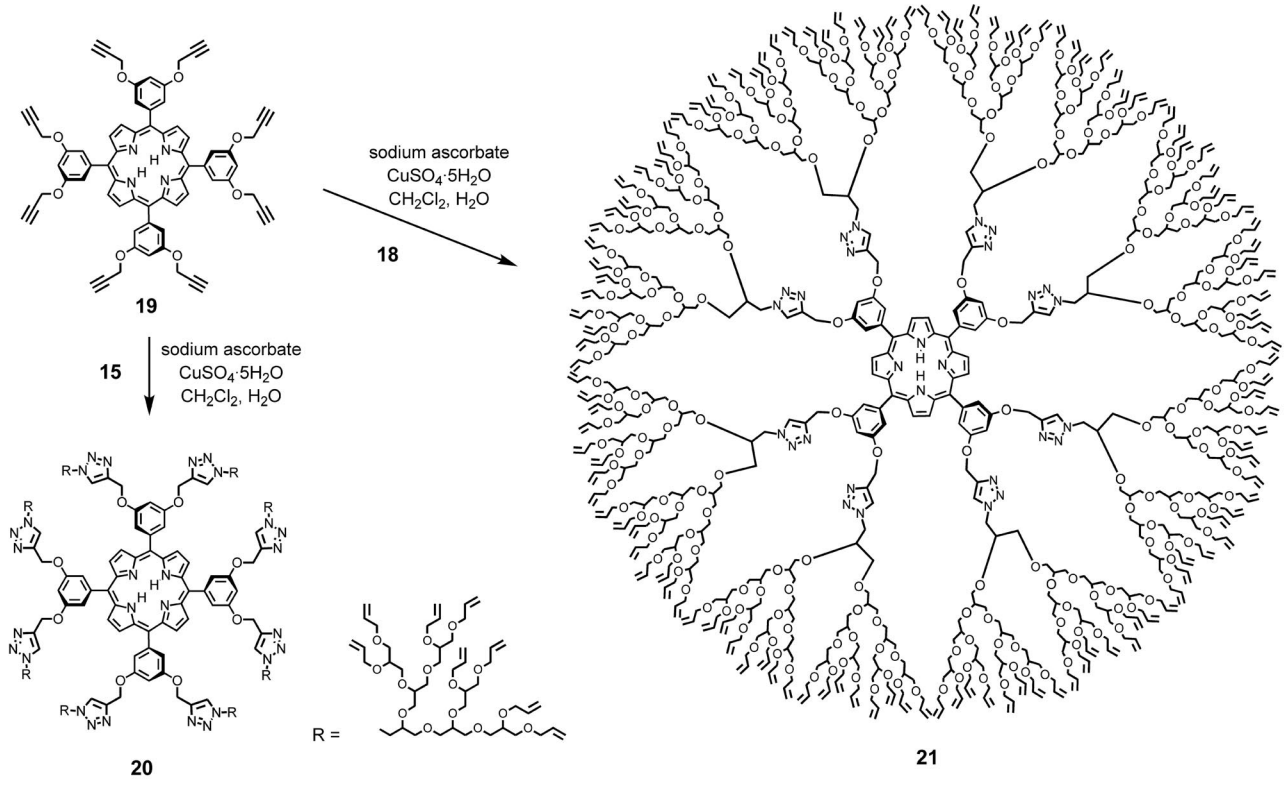


Figure 1. MALDI-TOF-MS spectra of dendron a) **13**, b) **15**, c) **16**, and d) **18**.



Scheme 4. Synthesis of dendrimers **20** and **21** using click chemistry and porphyrin core **19**.

Scheme 3). Dendrons **9** and **12** could also be converted into the [G-3.5]-azide **15** and the [G-4.5]-azide **18** using a two-step approach with tosylation followed by sodium azide displacement, the desired products obtained in an overall yield of 70% and 27%, respectively. Identification of the focal group functionality by ^{1}H and ^{13}C NMR as well as by ESI-MS and MALDI-TOF-MS facilitated the characterization of these compounds. In $CDCl_3$ the carbon adjacent to the alcohol group was readily distinguished from the carbon peak adjacent to the azide or the alkyne groups by ^{13}C NMR spectroscopy. In the ^{13}C NMR spectrum the carbon adjacent to the alcohol exhibited a peak at δ = 62.6 ppm as compared to the peaks at δ = 58.8 and 52.1 ppm for the carbons adjacent to the alkyne and azide, respectively. The molecular weight determinations for the 3rd and 4th generation azide and alkyne dendrons were confirmed by MALDI-TOF-MS. Thus, shown in Figure 1 are the spectra with peaks corresponding primarily to the sodium and potassium adducts of **13**, **15**, **16** and **18**.

A copper-catalyzed 1,3-dipolar cycloaddition was induced between porphyrin core **19** containing eight alkyne groups and azides [G-3.5]-**15** and [G-4.5]-**18** (Scheme 4). The porphyrin was chosen as a conveniently prepared, multivalent core with a strong UV/Vis signal. Additionally, there has been considerable interest in dendritic porphyrins.[24]

The crude products were purified by silica gel chromatography followed by preparative SEC chromatography, affording the desired dendrimers **20** and **21** in 65% and 66% yield, respectively. The ^{1}H NMR spectra were consistent with the assigned structures, but the dendrimers were best characterized by MALDI-TOF-MS and analytical SEC. As seen in Figure 2 (a), dendrimer **20** appears to be homogeneous with a full eight attachments present. Typical for highly branched macromolecules the SEC determined molecular weight underestimates the actual value. The SEC does show the presence of dimer, which reflects the beginning of the oligomerization observed with all of the polyallyl polyglycerol dendrimers unless care is taken to exclude oxygen. Alternatively, the alkene groups may be dihydroxylated to provide stable material, something that was observed with the dendrons, but not yet examined with the dendrimers. Dendrimer **21** was observed by MALDI-TOF-MS to contain a mixture of 6, 7, and 8 attachments, with the latter predominating. (Figure 2, c). Nonetheless, the measured PDI was quite low (Figure 2, d).

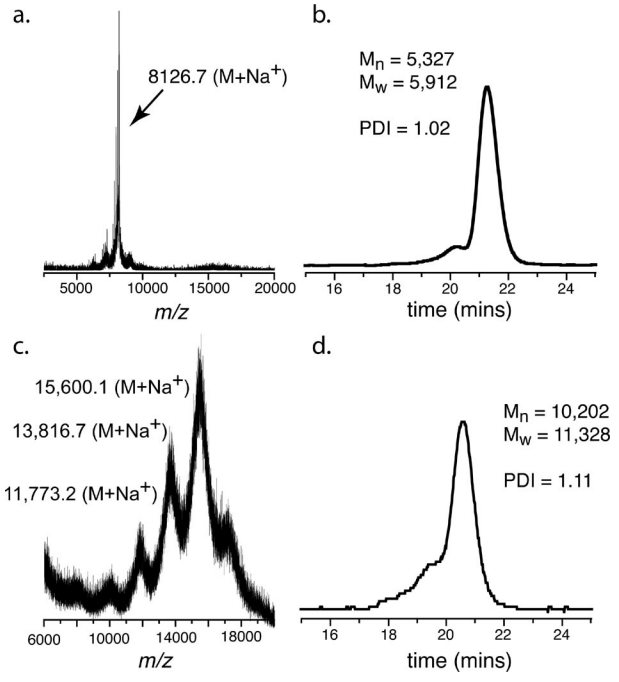


Figure 2. MALDI-TOF-MS spectra of dendrimers (a) **20** and (c) **21** and analytical SEC chromatograms of (b) **20** and (d) **21**.

Conclusions

Polyether dendrons containing a TBDPS protecting group have been synthesized in high yield and high purity. The synthesis proceeds very rapidly and purification by column chromatography is only necessary after the allylation steps. After deprotection of the TBDPS group, the focal point of the polyether dendrons can be readily converted to a wide variety of functional groups including the azide and alkyne group. Dendrons containing azide focal points have been shown to attach to polyalkynyl cores in good yields using the copper-catalyzed 1,3-dipolar cycloaddition ("click") reaction. Even highly congested, high molecular weight dendrimers such as **21** with 128 allyl ether groups on their periphery can be made in this manner. Overall, the chemistry is likely to be particularly useful both for making biocompatible nanostructures and for mono-molecular imprinting.[25]

Experimental Section

General Dihydroxylation Procedure: The allyl compound was vigorously stirred in a 5:3:1 acetone/water/*tert*-butyl alcohol mixture at a concentration of 0.6 M at room temperature under ambient atmosphere. To this was added a 50 wt.-% solution of *N*-methylmorpholine *N*-oxide (NMO) in water (1.10 mmol per alkene) followed by OsO_4 (0.25 mol-% per alkene). When the starting material had disappeared according to TLC analysis, the solvents were removed in vacuo at 50 °C. The residue was evaporated twice at 40 °C with toluene in vacuo to give the crude product as a brown viscous oil.

General NaH Allylation Procedure: To the crude diol was added allyl bromide, tetrabutylammonium iodide (TBAI) and THF. The reaction vessel was cooled to 0 °C and NaH (60% in mineral oil) was added slowly with vigorous stirring. The reaction vessel was warmed to room temperature. After 20 h water was added and the dendrimer extracted with EtOAc.

3-(*tert*-Butyl-diphenyl-silyloxy)propane-1,2-diol (3): To 5.6 g of **2**, was added 2.3 g (14 mmol) NMO, 9 mL acetone, 9 mL H_2O, 1.8 mL *tert*-butyl alcohol and 0.3 mL OsO_4 (4 wt.-% in H_2O). Using the general dihydroxylation procedure, a brown oil was obtained that could be used in the next step without purification. Extracted with EtOAc (3 × 100 mL), dried with sodium sulfate, filtered and evaporated to obtain 6.0 g (96%) of a beige solid. ^{1}H

NMR ($CDCl_3$, 400 MHz): δ = 7.67 (m, 4 H), 7.42 (m, 6 H), 3.81 (m, 1 H), 3.69 (m, 4 H), 2.71 (d, J = 4.8 Hz, 1 H), 2.20 (t, J = 4.8 Hz, 1 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 135.8, 133.1, 130.2, 128.1, 72.1, 65.5, 64.1, 27.1, 19.5 ppm. MS (ESI): m/z = 331.5 [MH^+].

[2,3-Bis(allyloxy)propoxy]-*tert*-butyl-diphenylsilane (4): To 2.8 g (8.3 mmol) of the crude diol **3** in 20 mL THF was added 12 mL (0.14 mol) allyl bromide and 14 mg (0.039 mmol) TBAI. Using the general NaH allylation procedure, obtained a crude brown oil. Purified using column chromatography (silica gel, 9:1 PE/EtOAc) to obtain 3.1 g (91%) of **4** as a white solid. ^1H NMR ($CDCl_3$, 400 MHz): δ = 7.71 (m, 4 H), 7.42 (m, 6 H), 5.92 (ddt, J = 17.2, 14.4, 10.4, 4.8 Hz, 2 H), 5.28 (ddt, J = 17.2, 6.6, 1.6 Hz, 2 H), 5.17 (ddt, J = 14.4, 10.4, 1.6 Hz, 2 H), 4.11 (m, 2 H), 4.03 (m, 2 H), 3.77 (m, 2 H), 3.67 (m, 2 H), 3.58 (m, 1 H), 1.08 (s, 9 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 135.9, 135.5, 135.1, 133.9, 129.9, 127.9, 117.1, 117.0, 78.9, 72.6, 71.6, 70.4, 63.6, 27.1, 19.5 ppm. MS (ESI): m/z = 433.3 [M + Na^+].

3-{2-(*tert*-Butyl-diphenylsilyloxy)-1-[(2,3-dihydroxypropoxy)methyl]-ethoxy}propane-1,2-diol (5): To 6.5 g (0.016 mol) of **4** was added 5.6 g (0.048 mol) NMO, 0.3 mL OsO_4 (4 wt.-% in H_2O), 9 mL acetone, 9 mL H_2O and 1.8 mL *tert*-butyl alcohol. Using the general dihydroxylation procedure, obtained a white solid that could be used in the next step without purification. Extracted with EtOAc (3 × 100 mL), dried with sodium sulfate, filtered and evaporated to obtain 7.0 g (92%) of a yellow oil. ^1H NMR ($CDCl_3$, 400 MHz): δ = 7.65 (m, 4 H), 7.40 (m, 6 H), 4.20 (m, 2 H), 3.82 (m, 2 H), 3.58 (m, 15 H), 1.05 (s, 9 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 135.8, 133.3, 130.1, 128.0, 80.6, 80.3, 78.0, 73.4, 73.1, 72.8, 72.3, 71.6, 71.1, 70.9, 70.8, 64.3, 64.2, 64.0, 63.5, 27.0, 19.4 ppm. MS (ESI): m/z = 501.3 [M + Na^+].

2,3-Bis{[2,3-bis(allyloxy)propoxy]propoxy}-*tert*-butyl-diphenylsilane (6): To 5.5 g (12 mmol) of the crude diol **5** was added 45 mL (0.49 mol) allyl bromide and 24 mg (0.06 mmol) TBAI in 50 mL THF. Using the general allyation procedure, obtained a brown oil that was purified using column chromatography (silica gel, 9:1 PE/EtOAc) to afford 7.1 g (96%) of a light yellow oil. ^1H NMR ($CDCl_3$, 400 MHz): δ = 7.67 (m, 4 H), 7.39 (m, 6 H), 5.88 (m, 4 H), 5.24 (m, 4 H), 5.14 (m, 4 H), 4.11 (m, 4 H), 3.98 (m, 4 H), 3.70 (m, 2 H), 3.55 (m, 13 H), 1.05 (s, 9 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 135.8, 135.5, 135.4, 135.1, 135.0, 133.6, 129.9, 127.9, 118.2, 117.1, 117.0, 116.9, 80.4, 72.5, 71.9, 71.7, 71.6, 71.5, 70.6, 29.9, 27.0, 19.5 ppm. MS (ESI): m/z = 661.4 [M + Na^+].

3-[2-{2-[2,3-Bis(2,3-dihydroxypropoxy)propoxy]-3-(*tert*-butyl-diphenylsilyloxy)propoxy}-1-(2,3-dihydroxypropoxymethyl)ethoxy]-propane-1,2-diol (7): To 3.3 g (5.1 mmol) of **6** was added 3.6 g (30.7 mmol) NMO, 0.2 mL OsO_4 (4 wt.-% in H_2O), 7 mL acetone, 7 mL H_2O and 4 mL *tert*-butyl alcohol. Using the general dihydroxylation procedure, obtained a crude brown oil that could be used in the next step without purification. Extracted with 9:1 $CHCl_3$/2-propanol (3 × 200 mL), dried with sodium sulfate, filtered and evaporated to obtain 3.9 g (98%) of a yellow oil. ^1H NMR ($CDCl_3$, 400 MHz): δ = 7.66 (m, 4 H), 7.41 (m, 6 H), 4.66 (br. s, 3 H), 4.22 (br. s, 3 H), 3.85 (m, 2 H), 3.56 (m, 35 H), 1.05 (s, 9 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 135.8, 133.4, 130.1, 128.0, 80.6, 78.9, 78.7, 73.0, 72.2, 72.1, 71.9, 71.8, 71.7, 71.4, 71.3, 71.2, 71.1, 70.9, 63.9, 63.7, 63.4, 63.3, 27.1, 19.4 ppm. MS (ESI): m/z = 797.6 [M + Na^+].

{2,3-Bis(2,3-bis[2,3-bis(allyloxy)propoxy]propoxy)propoxy}-*tert*-butyl-diphenylsilane (8): To 1.0 g (1.3 mmol) of the crude brown oil **7** was added 8.0 mL (88 mmol) allyl bromide and 5.0 mg (0.014 mmol) TBAI in 9 mL THF. Using the general NaH allylation procedure, obtained a crude brown oil. Purified using column chromatography (silica gel, 9:1 PE/EtOAc to 4:1 PE/EtOAc) to afford 1.4 g (99%) of a light yellow oil. ^1H NMR ($CDCl_3$, 500 MHz): δ = 7.66 (m, 4 H), 7.38 (m, 6 H), 5.87 (m, 8 H), 5.24 (m, 8 H), 5.12 (m, 8 H), 4.12 (m, 8 H), 3.97 (m, 8 H), 3.57 (m, 35 H), 1.04 (s, 9 H) ppm. ^{13}C NMR ($CDCl_3$, 126 MHz): δ = 135.8, 135.5, 135.1, 135.0, 129.9, 127.9, 117.1, 117.0, 116.9, 116.8, 79.1, 77.6, 77.5, 77.3, 77.2, 72.5, 72.0, 71.8, 71.5, 71.4, 70.6, 70.5, 70.4, 27.0, 19.4 ppm. MS (MALDI-TOF-MS): m/z = 1117.8 [M + Na^+], 1134.2 [M + K^+].

2,3-Bis{2,3-bis[2,3-bis(allyloxy)propoxy]propoxy}propan-1-ol (9): To 0.55 g (0.50 mmol) of **8** in 6 mL THF was added 2.0 mL (2.0 mmol) of TBAF (1.0 M in THF). After 20 h evaporated to remove residual solvent. Extracted with EtOAc (3 × 50 mL), washed with 50 mL H_2O, dried with sodium sulfate, filtered and the solvents evaporated. Purified using column chromatography [silica gel, 9:1 PE/EtOAc (0.5 L), 1:1 PE/EtOAc (0.5 L)] to obtain 0.42 g (98%) of a light yellow oil. ^1H NMR ($CDCl_3$, 500 MHz): δ = 5.90 (m, 8 H), 5.27 (m, 8 H), 5.16 (m, 8 H), 4.13 (m, 8 H), 3.99 (m, 8 H), 3.65 (m, 12 H), 3.53 (m, 23 H) ppm. ^{13}C NMR ($CDCl_3$, 126 MHz): δ = 135.3, 135.4, 135.0, 134.9, 117.1, 117.0, 77.5, 77.3, 77.2, 72.6, 72.5, 71.9, 71.6, 71.5, 70.7, 70.4, 70.3, 70.0, 53.5 ppm. MS (ESI): m/z = 857.7 [MH^+].

3-{3-[3-(2-{2,3-Bis[2,3-bis(2,3-dihydroxypropoxy)propoxy]propoxy}-3-(*tert*-butyl-diphenylsilyloxy)propoxy)-2-[2,3-bis(2,3-dihydroxy)-propoxy]propoxy]propoxy}-2-(2,3-dihydroxypropoxy)propoxy]-propane-1,2-diol (10): To 2.2 g (2.0 mmol) of **8** was added 2.9 g (25 mmol) NMO, 0.5 mL OsO_4 (4 wt.-% in H_2O), 9 mL acetone, 9 mL H_2O and 3.0 mL *tert*-butyl alcohol. After 20 h evaporated off solvents leaving a minimal amount of H_2O. Extracted with 9:1 $CHCl_3$/2-propanol (3 × 200 mL), dried with sodium sulfate, filtered and evaporated to afford 3.1 g (91%) of a yellow oil. ^1H NMR (DMSO, 500 MHz): δ = 7.64 (m, 4 H), 7.45 (m, 6 H), 4.60 (m, 16 H), 3.50 (m, 75 H), 0.99 (s, 9 H) ppm. ^{13}C NMR (DMSO, 126 MHz): δ = 140.7, 140.5, 135.3, 133.3, 78.3, 77.1, 77.0, 76.3, 76.2, 75.9, 68.5, 32.0, 24.2 ppm. MS (MALDI-TOF-MS): m/z = 1390.3 [M + Na^+].

[2,3-Bis{2,3-bis(2,3-bis[2,3-bis(allyloxy)propoxy]propoxy)propoxy}-propoxy]-*tert*-butyl-diphenylsilane (11): To 3.1 g (2.2 mmol) of **10** was added 26 mL (0.29 mmol) allyl bromide and 9.1 mg (0.025 mmol) TBAI in 30 mL DMF. Using the general allylation procedure, obtained a brown oil that was purified using column chromatography [silica gel, 9:1 PE/EtOAc (1.0 L), 4:1 PE/EtOAc (1.0 L), 1:1 PE/EtOAc (1.0 L)] to afford 2.7 g (66%) of a light yellow oil. ^1H NMR ($CDCl_3$, 500 MHz): δ = 7.65 (m, 4 H), 7.38 (m, 6 H), 5.88 (m, 16 H), 5.25 (m, 16 H), 5.14 (m, 16 H), 4.11 (m, 16 H), 3.98 (m, 16 H), 3.54 (m, 75 H), 1.04 (s, 9 H) ppm. ^{13}C NMR ($CDCl_3$, 126 MHz): δ = 135.8, 135.6, 135.5, 135.1, 135.0, 129.9, 128.0, 117.1, 117.0, 116.9, 116.8, 79.1, 78.9, 72.5, 72.0, 71.9, 71.7, 71.5, 70.7, 70.6, 70.5, 27.1, 19.5 ppm. MS (MALDI-TOF): m/z = 2031.7 [M + Na^+], 2047.9 [M + K^+].

3-[2-Allyloxy-3-(2-[2,3-bis(allyloxy)propoxy]-3-{2-(2,3-bis[2,3-bis-(allyloxy)propoxy]propoxy)-3-prop-2-ynyloxypropoxy}propoxy)-propoxy]propan-1-ol (12): To 2.02 g (1.0 mmol) of **11** in 5.0 mL THF was added 4.0 mL of TBAF (1.0 M in THF). After 20 h evaporated to remove residual solvent. Extracted with EtOAc (3 × 50 mL), washed with 50 mL H_2O, dried with sodium sulfate, filtered and the solvents evaporated. Purified using column chromatography [silica gel, 9:1 PE/EtOAc (0.5 L), 1:1 PE/EtOAc (0.5 L)] to obtain 1.64 (92%) of a light yellow oil. ^1H NMR ($CDCl_3$, 500 MHz): δ = 5.88 (m, 16 H), 5.25 (m, 16 H), 5.14 (m, 16 H), 4.11 (m, 16 H), 3.98 (m, 16 H), 3.54 (m, 75 H), 2.96 (s, 1

H) ppm. ^{13}C NMR ($CDCl_3$, 126 MHz): δ = 135.8, 135.6, 135.5, 135.1, 135.0, 117.1, 117.0, 116.9, 116.8, 79.1, 78.9, 72.5, 72.0, 71.9, 71.7, 71.5, 70.7, 70.6, 70.5 ppm. MS (MALDI-TOF): *m/z* = 1792.3 [M + Na^+], 2047.9 [M + K^+].

3-[2-Allyloxy-3-(2-[2,3-bis(allyloxy)propoxy]-3-{2-(2,3-bis[2,3-bis-(allyloxy)propoxy]propoxy)-3-prop-2-ynyloxypropoxy}propoxy)-propoxy]propene (13): To 0.51 g (0.59 mmol) of **9** was added 0.53 mL (4.8 mmol) propargyl bromide (80 wt.-% in toluene) and 24 mg (0.065 mmol) TBAI in 5 mL THF. The reaction vessel was cooled to 0 °C and 78 mg (2.0 mmol) of sodium hydride (60 wt.-% in mineral oil) was added slowly. The reaction vessel was warmed to room temperature. After 16 h added 20 mL H_2O and evaporated off solvent. Extracted with EtOAc (3 × 50 mL), washed with 50 mL H_2O, dried with sodium sulfate, filtered and the solvents evaporated. Purified using column chromatography (silica gel, 9:1 PE/EtOAc to 1:1 PE/EtOAc) to afford 0.48 g (91%) of a light yellow oil. ^1H NMR ($CDCl_3$, 400 MHz): δ = 5.90 (m, 8 H), 5.26 (m, 8 H), 5.15 (m, 8 H), 4.15 (d, *J* = 1.6 Hz, 2 H), 4.13 (m, 8 H), 3.99 (m, 8 H), 3.65 (m, 11 H), 3.53 (m, 24 H), 2.43 (t, *J* = 1.6 Hz, 1 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 135.6, 135.5, 135.1, 135.0, 117.1, 117.0, 116.9, 116.8, 116.7, 79.9, 79.0, 78.8, 78.6, 77.2, 74.8, 72.5, 72.0, 71.9, 71.8, 71.7, 71.5, 71.3, 71.2, 70.7, 70.6, 70.5, 70.0, 58.8 ppm. MS (ESI): *m/z* = 917.7 [M + Na^+].

2,3-Bis{2,3-bis[2,3-bis(allyloxy)propoxy]propoxy}propyl Toluene-4-sulfonate (14): To 0.70 g (0.82 mmol) of **9** in 5 mL CH_2Cl_2 was added 0.32 g (1.7 mmol) of tosyl chloride and 0.46 mL (3.3 mmol) triethylamine. After 20 h added 20 mL H_2O and evaporated off solvents. Extracted with EtOAc (3 × 75 mL), washed with 75 mL H_2O, dried with sodium sulfate, filtered and the solvents evaporated. Purified using column chromatography [silica gel, 9:1 PE/EtOAc (0.5 L), 4:1 PE/EtOAc (0.5 L) and 7:3 PE/EtOAc (0.5 L)] to obtain 0.70 g (84%) of a light yellow oil. ^1H NMR ($CDCl_3$, 400 MHz): δ = 7.77 (d, *J* = 8.0 Hz, 2 H), 7.33 (d, *J* = 8.0 Hz, 2 H), 5.89 (m, 8 H), 5.25 (m, 8 H), 5.14 (m, 8 H), 4.12 (m, 9 H), 3.98 (m, 9 H), 3.63 (m, 9 H), 3.50 (m, 24 H), 2.43 (s, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 145.0, 135.5, 135.4, 135.0, 133.2, 130.1, 128.2, 117.2, 117.1, 117.0, 78.9, 78.7, 77.5, 77.2, 77.1, 77.0, 72.6, 72.5, 71.9, 71.8, 71.5, 71.4, 70.7, 70.6, 70.4, 70.3, 70.1, 21.9 ppm. MS (MALDI-TOF): *m/z* = 1034.4 [M + Na^+], 1050.2 [M + K^+].

3-(2-Allyloxy-3-[3-{3-azido-2-(2,3-bis[2,3-bis(allyloxy)propoxy]-propoxy)propoxy}-2-(2,3-bis(allyloxypropoxy)propoxy]propoxy)-propene (15): To 1.1 g of **14** in 12 mL DMF was added 0.29 g (4.5 mmol) of sodium azide. The reaction was heated to 80 °C. After 20 h added 100 mL H_2O, extracted with EtOAc (3 × 50 mL), washed with H_2O (2 × 100 mL), dried with sodium sulfate, filtered and the solvents evaporated. Obtained 0.89 g (91%) of a light yellow oil. ^1H NMR ($CDCl_3$, 400 MHz): δ = 5.88 (m, 8 H), 5.25 (m, 8 H), 5.14 (m, 8 H), 4.12 (m, 8 H), 3.98 (m, 8 H), 3.56 (m, 34 H), 3.35 (m, 1 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 135.5, 135.4, 135.0, 134.9, 117.0, 116.9, 116.8, 78.9, 78.6, 77.5, 72.5, 72.4, 71.9, 71.8, 71.5, 71.4, 70.7, 70.6, 70.5, 70.4, 70.3, 52.1 ppm. MS (ESI): *m/z* = 904.5 [M + Na^+].

Dendron (16): To 0.20 g (0.12 mmol) of **12** was added 0.10 mL (1.1 mmol) propargyl bromide (80 wt.-% in toluene) and 5.5 mg (0.015 mmol) TBAI in 3 mL THF. The reaction vessel was cooled to 0 °C and 24 mg (0.59 mmol) of sodium hydride (60 wt.-% in mineral oil) was added slowly. The reaction vessel was warmed to room temperature. After 16 h added 20 mL H_2O and evaporated off solvent. Extracted with EtOAc (3 × 50 mL), washed with 50 mL H_2O, dried with sodium sulfate, filtered and the solvents evaporated. Purified using column chromatography (silica gel, 9:1 PE/EtOAc to 1:1 PE/EtOAc) to afford 0.15 g (69%) of a light yellow oil. ^1H NMR ($CDCl_3$, 500 MHz): δ = 5.89 (m, 16 H), 5.26 (m, 16 H), 5.14 (m, 16 H), 4.15 (d, *J* = 1.5 Hz, 2 H), 4.11 (m, 16 H), 3.99 (m, 16 H), 3.54 (m, 75 H), 2.43 (t, *J* = 1.5 Hz, 1 H) ppm. ^{13}C NMR ($CDCl_3$, 126 MHz): δ = 135.8, 135.6, 135.5, 135.1, 135.0, 117.1, 117.0, 116.9, 116.8, 79.1, 78.9, 72.5, 72.0, 71.9, 71.7, 71.5, 70.7, 70.6, 70.5, 58.8 ppm. MS (MALDI-TOF): *m/z* = 1807.2 [M + Na^+], 1823.3 [M + K^+].

3-(2-Allyloxy-3-[2-(2,3-bis(allyloxy)propoxy]-3-{2-[2,3-bis[2,3-bis-(allyloxy)propoxy]propoxy)-3-prop-2-ynyloxypropoxy}propoxy)-propoxy]propyl Toluene-4-sulfonate (17): To 4.2 g (2.35 mmol) of **12** was added 2.325 g (12 mmol) tosyl chloride and 2 mL (14 mmol) triethylamine in 20 mL CH_2Cl_2. The mixture was stirred at room temperature overnight. The mixture was diluted with H_2O (50 mL) and extracted with CH_2Cl_2 (3 × 100 mL). The organic layer was dried with $MgSO_4$, filtered, and concentrated under vacuum. The crude material was purified by column chromatography (silica gel, 2:1 PE/EtOAc to EtOAc) to afford a 4.198 g (93%) of yellow oil ^1H NMR ($CDCl_3$, 500 MHz): δ = 7.78 (d, *J* = 8.0 Hz, 2 H), 7.34 (d, *J* = 8.0 Hz, 2 H), 5.89 (m, 16 H), 5.26 (m, 16 H), 5.14 (m, 16 H), 4.13 (d, *J* = 4.8 Hz, 16 H), 3.99 (d, *J* = 4.8 Hz, 16 H), 3.73–3.33 (m, 75 H), 2.44 (s, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 126 MHz): δ = 144.8, 135.4, 135.3, 134.9, 134.8, 129.9, 128.0, 116.9, 116.8, 116.7, 116.6, 78.9, 78.6, 78.4, 72.3, 71.8, 71.7, 71.6, 71.4, 71.3, 70.5, 70.4, 70.3, 70.2, 69.6, 69.5 ppm. MS (MALDI-TOF): *m/z* = 1946.21 [M + Na^+], 1962.3 [M + K^+].

Dendron 18: To 4.2 g (2.2 mmol) of **17** in 30 mL DMF was added 0.73 g (11.23 mmol) of sodium azide. The reaction was heated to 40 °C. After 23 h added 2 N NaOH (50 mL) and extracted with EtOAc (3 × 75 mL). The organic layer was washed with H_2O (75 mL), washed with brine (75 mL), dried with $MgSO_4$, filtered, and concentration under vacuum. The crude material was purified by column chromatography (silica gel, 2:1 PE/EtOAc to 1:2 PE/EtOAc) to afford 1.136 g (29%) viscous yellow oil. ^1H NMR ($CDCl_3$, 500 MHz): δ = 5.91 (m, 16 H), 5.28 (m, 16 H), 5.17 (m, 16 H), 4.15 (d, *J* = *5.3 Hz*, 16 H), 4.01 (d, *J* = *2.3 Hz*, 16 H), 3.73–3.39 (m, 75 H) ppm. ^{13}C NMR ($CDCl_3$, 126 MHz): δ = 135.5, 135.4, 135.0, 117.1, 117.0, 116.9, 79.1, 78.8, 72.6, 72.5, 71.9, 71.6, 71.5, 70.5, 70.4 ppm. MS (MALDI-TOF): *m/z* = *m/z* 1816.5 [M + Na^+].

Porphyrin Click Dendron Core 19: To 0.27 g (0.37 mmol) of 5,10,15,20-tetrakis(3′,5′-dihydroxyphenyl)porphyrin and 1.32 g (9.5 mmol) of K_2CO_3 in 5 mL DMF was added. To the DMF solution, propargyl bromide (80 wt.-%) in toluene solution (0.7 mL) was added. The mixture was stirred at room temperature overnight. The resulting crude solid was diluted with 2 N NaOH (25 mL) and extracted with CH_2Cl_2 (2 × 100 mL). The organic layer was washed with water (50 mL) and brine (50 mL), dried with Na_2SO_4, filtered, and concentrated under vacuum. The crude material was purified by column chromatography (silica gel, CH_2Cl_2) to afford 0.21 g (54%) of purple solid. ^1H NMR ($CDCl_3$, 500 MHz): δ = 8.95 (s, 8 H), 7.51 (d, *J* = 2.3 Hz, 8 H), 7.07 (t, *J* = 2.3 Hz, 4 H), 4.88 (d, *J* = 2.3 Hz, 16 H), 2.60 (t, *J* = 2.3 Hz, 8 H), –2.88 (s, 2 H) ppm. ^{13}C NMR ($CDCl_3$, 126 MHz): δ = 157.0, 144.2, 119.6, 115.5, 102.4, 78.6, 76.2, 56.4 ppm. HRMS (ESI): *m/z* = 1047.3 [MH^+]. $C_{68}H_{46}N_4O_8$ (1047.13): calcd. C 78.00, H 4.43, N 5.35; found C 77.63, H 4.23, N 5.38.

Porphyrin Dendrimer 20: To 0.53 g (0.601 mmol) of **15** and 0.062 g (0.059 mmol) of **19** in 10 mL CH_2Cl_2/H_2O (1:1, v/v), 0.074 g (0.30 mmol) $CuSO_4 \cdot 2H_2O$ and 0.094 g (0.473 mmol) sodium-L-ascorbate were added. After 6 d, the mixture was diluted with H_2O (50 mL) and extracted with CH_2Cl_2 (3 × 50 mL). The organic layer

was dried with $MgSO_4$, filtered, and concentrated under vacuum. The crude was purified by column chromatography (silica gel, 1:1 PE/EtOAc to EtOAc to 4:1 EtOAc/MeOH) and by preparative SEC [Bio-Beads S-X1 200–400 mesh beads (Bio-Rad), toluene] to afford a viscous dark purple oil. ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.89 (s, 8 H), 5.84 (m, 64 H), 5.36–4.87 (m, 128 H), 4.59 (s, 16 H), 4.24–3.77 (m, 128 H), 3.75–3.22 (m, 266 H) ppm. ^{13}C NMR ($CDCl_3$, 126 MHz): δ = 135.4, 134.9, 117.1, 117.0, 116.9, 78.7, 72.5, 72.3, 71.9, 71.4, 70.8, 70.7, 70.5, 70.3, 70.8, 70.2, 70.1 ppm. MS (MALDI-TOF): m/z = 8126.7 [M + Na^+].

Porphyrin Dendrimer 21: To 0.487 g (0.271 mmol) of **18** and 0.033 g (0.031 mmol) of **19** in 18 mL CH_2Cl_2/H_2O (1:1, v/v), 0.14 g (0.58 mmol) $CuSO_4{\cdot}2H_2O$ and 0.114 g (0.575 mmol) sodium-L-ascorbate were added. After 5 d, the mixture was diluted with H_2O (50 mL) and extracted with CH_2Cl_2 (5 × 50 mL). The organic layer was dried with $MgSO_4$, filtered, and concentrated under vacuum. The crude was purified by column chromatography (silica gel, CH_2Cl_2 to 95:5 CH_2Cl_2/MeOH) and preparative SEC [Bio-Beads S-X1 200–400 mesh beads (Bio-Rad), toluene] to afford a viscous dark purple oil. Although **21** is a mixture, the NMR spectrum showed peaks consistent with product, presumably as a result of similar chemical shifts for the various products. ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.89 (s, 8 H), 5.87 (m, 128 H), 5.44–4.94 (m, 256 H), 4.58 (s, 16 H), 4.27–3.82 (m, 256 H), 3.78–3.20 (m, 586 H) ppm. ^{13}C NMR ($CDCl_3$, 126 MHz): δ = 135.5, 135.0, 134.9, 117.1, 116.9, 116.8, 77.9, 76.7, 72.4, 71.8, 71.7, 71.4, 71.3, 70.6, 70.4 ppm. MS (MALDI-TOF): m/z = 15600.1 [M + Na^+].

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